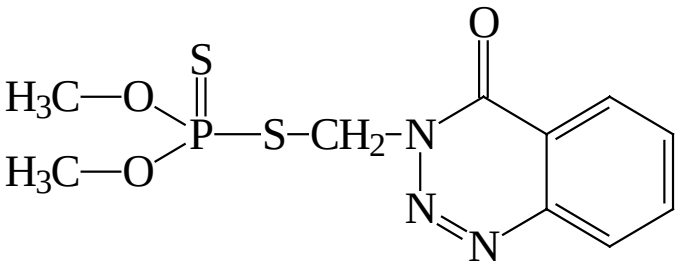
EVALUATION OF AZINPHOS-METHYL AS A TOXIC AIR CONTAMINANT



Part D

DPR Staff Responses to Comments

California Environmental Protection Agency
Sacramento, California

July 2000

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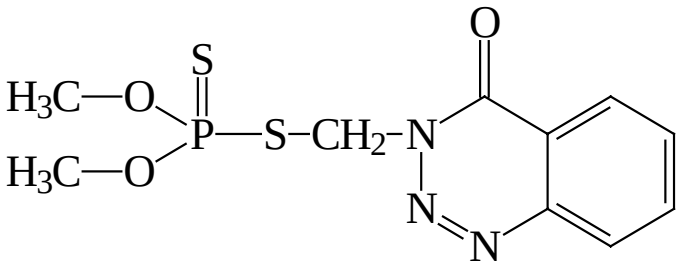

Part D
DPR Staff Responses to Comments

California Department of Pesticide Regulation

California Environmental Protection Agency
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I. Written Comments Received on the November 1999 Draft Version of the Evaluation of Azinphos-methyl as a Toxic Air Contaminant

A. Lynton Baker, Program Assistance Section, Stationary Source Division, California Air Resources Board (December, 28, 1999)

B. Anna M. Fan, Ph.D., Chief, Pesticide and Environmental Toxicology Section, California Office of Environmental Health Hazard Assessment (April 13, 2000)

II. Department of Pesticide Regulation Staff Responses to Summarized Comments on the Executive Summary

Comment 1: We recommend that the section on azinphos-methyl use include the chief uses and amounts applied in 1998, and note that the annual statewide use has dropped from a high of about 520,00 pounds in 1992 to about 193,000 pounds in 1998. (Baker, December 28, 1999)

Response: The chief uses and amounts of azinphos-methyl applied in 1998 was added, and the drop in annual use from 1992 to 1998 was noted.

Comment 2: We recommend summarizing the 1999 voluntary use restrictions accepted by the U.S. EPA in the report. Note how these restrictions may reduce air concentrations of azinphos-methyl in California, and whether they apply to almonds. (Baker, December 28, 1999)

Response: A summary of the 1999 voluntary azinphos-methyl use restrictions accepted by the U.S. EPA was included in section II-B, and how air concentrations may be reduced in California was noted. The restrictions do not apply to almonds.

Comment 3: There are two minor discrepancies in the section that summarizes the ambient air monitoring conducted in Kern County in 1987: 1) the dates of the monitoring were June 22 – July 16, 1987, and 2) the minimum detection limit was 0.022 $\mu g/m^3$. We also recommend noting in the paragraph summarizing the application site monitoring that the application took between 1.5 and 2 hours, for a total sampling interval of 2.5 – 3 hours. (Baker, December 28, 1999)

Response: The minor discrepancies in this section were corrected, and the recommended note on the application time was included.

Comment 4: In the section summarizing expected human exposures, we recommend including a statement as to whether the portion of Kern County mentioned

still represents the area of "greatest potential exposure" and whether current use patterns and rates per acre have changed since the time of ambient monitoring. (Baker, December 28, 1999)

Response: Use report data on a section basis for the portion of Kern County mentioned is not available for 1987. A comparison of 1987 and current use patterns is, therefore, not possible. Rates of azinphos-methyl per acre have not changed since the time of the ambient monitoring.

Comment 5: The section summarizing the potential health hazards of degradation products includes the statement "none of the air monitoring studies for azinphos-methyl analyzed for any degradation products". We request that this statement be clarified to indicate that neither of the monitoring requests (1987 ambient monitoring and 1988 application site monitoring requests) from DPR to ARB requested analysis for any degradation products. (Baker, December 28, 1999)

Response: The statement "none of the air monitoring studies for azinphos-methyl analyzed for any degradation products" was deleted from this section.

III. Department of Pesticide Regulation Staff Responses to Summarized Comments on Part A—Environmental Fate

Comment 1: We recommend noting that the concentrations in µg detected downwind in Table IV-3 are deposition concentrations, not air concentrations. (Baker, December 28, 1999)

Response: Table IV-3 was revised to reflect this recommendation.

Comment 2: We recommend including the mean ambient concentrations in Table IV-4. (Baker, December 28, 1999)

Response: A column of mean ambient concentrations in $\mu g/m^3$ was added to Table IV-4.

Comment 3: The monitoring site located at the Pond School is described as having "represented the 'worst-case situation' because almond orchards were located directly to the east, south, and west less than 100 meters from the air samplers". No information was collected by ARB's contractor regarding whether azinphos-methyl was applied to the almond orchards that surrounded the Pond School during the monitoring period. We recommend restating this as the Pond School having represented the "potential Worst-case situation". (Baker, December 28, 1999)

Response: The description of the Pond School monitoring site was restated to reflect this recommendation.

Comment 4: We recommend including the size of the orchard in the section summarizing the application site monitoring. We also recommend including the distances from the edge of the orchard to the sampling sites in Table IV-5. (Baker, December 28, 1999)

Response: The application monitoring section and Table IV-5 were revised to reflect these recommendations.

Comment 5: We recommend including a brief summary of the sampling method, flow rates, and analysis methods in the sections summarizing the ambient and application site monitoring. (Baker, December 28, 1999)

Response: A summary of the sampling method, flow rates, and analysis methods was included in section IV-E.

IV. Department of Pesticide Regulation Staff Responses to Summarized Comments on Part B—Exposure Assessment

Comment 1: On page 5, the ambient air sampling is described as having used " high volume air samplers." As noted in comments # 9 above, the ambient sampling flow rates were 2 liters per minutes. These are low volume air samplers. On the bottom of page 5, the sampling method is described as using "XAD-2 resin tubes with Teflon pre-filters". The text states that " except for one sample, all azinphos-methyl was trapped on the Teflon filters." This statement is misleading and implies that there was breakthrough from one pre-filter to the XAD-2 resin. During the ambient study, one sampling site had collocated samplers, one sampler with and one sampler without pre-filters. The one sample that contained azinphos-methyl in the XAD-2 resin tube was one of the samples without a pre-filter; the collocated sampler with a Teflon pre-filter also trapped azinphos-methyl. We recommend clarifying this statement. (Baker, December 28, 1999)

Response: The text was revised to indicate that low volume air samplers were used. In addition, the text was also revised to indicate that the one sample that did not trap azinphos-methyl in Teflon pre-filter in fact "was not equipped with a Teflon pre-filter."

Comment 2: Pages 8 and 10 list acute daily inhalation rates for a 6-year old child, adult male, and adult female as "16.7, 21.4, 11.4 m^3/day," respectively. A U.S. EPA Exposure Factors Handbook is listed as the reference. Similarly, chronic inhalation rates are listed as "10.0, 15.2, and 11.3 m^3/day," respectively. We recommend including a brief description of the assumed activity patterns that led to these inhalation rates, in particular the activity patterns that would lead to an adult female having an acute daily inhalation rate of slightly over half of an adult male and almost identical acute and chronic inhalation rates. (Baker, December 28, 1999)

Response: The U.S. EPA Exposure Factors Handbook calculated the above daily (acute) inhalation rates for each subgroup by summing the specific activity (resting, light, moderate, heavy) daily inhalation rates. The handbook suggested the above long-term (chronic) inhalation rates that were calculated based on oxygen consumption associated with average daily energy expenditure (food intake) for long periods of time. These statements were added to the text.

Comment 3: Concentrations of azinphos-methyl in ambient air used for exposure estimation in the TAC document are from an environmental monitoring study conducted in 1987. During that year, 154,655 pounds of azinphos-methyl were applied in Kern County where the monitoring study took place. We note that the amount of chemical applied in this county has more or less linearly declined since then, with 89,025 pounds of azinphos-methyl applied in 1998. Similarly, statewide use of azinphos-methyl has decreased recently, declining from 434,000 pounds in 1995 to 193,000 pounds in 1998. Based on the trends in use, the 1987 air concentrations of azinphos-methyl used in the exposure assessment might overestimate ambient air concentrations resulting from current use-patterns of azinphos-methyl. (Fan, April 13, 2000)

Response: The yearly use of AZM in California had been fairly steady from 1980 to 1996 (400,000 to 500,00 lb). The significant decline in 1998 may be due to some regulatory restrictions for worker safety that were imposed by DPR in 1998. While we agree that the 1987 air concentrations used in the exposure assessment might overestimate ambient air concentrations resulting from current use patterns (1997 and 1998), we believe that the future use trend is uncertain at this time. These statements have been clarified in the document.

Comment 4: The lowest estimated acute margin of exposure (MOE) in the draft TAC document is 830, which implies a significant margin of safety for the

general public following agricultural applications of azinphos-methyl. However, during the period 1987 through 1996, there were 36 cases of non-occupational illness associated with the use of azinphos-methyl. Two pesticide drift incidents, one in 1987 and one in 1993, were responsible for all but two of these cases. We recommend including more detailed discussion of the residential-drift incidents in the TAC document and address the risks associated with these types of exposures. Note that azinphos-methyl was one of only five organophosphate insecticides associated with a significant increase in systemic illnesses during the period 1984 to 1988 (Weinbaum et al., 1997). (Fan, April 13, 2000)

Response: The 1987 incident started with an application to an orchard nearby a residential area. Residents complaint to the police started with notice of odor. Police started the evacuation of the area. The evacuation was cancelled by the county health department because of no acute poisoning and no health hazard. None of the individuals who sought medical attention received any treatment. Odor was also the contributing factor in the 1993 incident. None of the individuals who sought medical attention immediately after the incident received acute poisoning treatment. Swab samples taken from the affected residential areas one and two days after the application were negative for AZM residues. The investigation concluded that there was no evidence of AZM drift. More information about these two incidents was added to the document. The risks associated with these types of exposures could be characterized from the information provided.

Comment 5: Body weights and inhalation rates used in the exposure calculations appear to be average values. We were able to verify some, but not all, of the values used in the draft TAC document by consulting the citation provided (U.S. EPA, 1997). For example, the inhalation rates of 15.2 and 11.3 m^3/day, which represent chronic inhalation rates for adult males and adult females, respectively, are average values and were easily found in the U.S.

Environmental Protection Agency's (U.S. EPA) 1997 document. We were unable to determine if the value of 10.0 m^3/day used for six-year-olds was also an average as we could not find it in the reference. Similarly, some discussion should be provided regarding the selection of the body weights used in the risk assessment. The rationale for using 95th percentile and maximum air concentrations for acute exposures (both offsite and ambient air concentrations) and average values for seasonal and chronic exposures to ambient air concentrations should also be stated. (Fan, April 13, 2000)

Response: The value of 10.0 m^3/day used for six-year-olds was also an average and is listed in the same Table of the referenced document (Table 5-23, Summary of Recommended Values for Inhalation, Long-term Exposure, children 6-8 years) that the values for adults are listed. The body weights are average values, taken from the reference (U.S. EPA document). These values do not seem to be highly debatable in favor of some other values that could drastically affect the dose estimates. Additional discussion of the body weight values in the document could add bulk but not much substance to the document.

The 95th percentile was selected to calculate an upper-bound acute exposure for a single day. The mean was selected since it was assumed that a person would be exposed every day to the corresponding concentration during the entire season. These explanations were added to the document. The selection of highest air concentration for offsite acute exposure is obvious, since the highest concentration was found to the north of the site (down wind).

Comment 6: Dermal exposure from airborne azinphos-methyl is not addressed in the document. This potential exposure route should be discussed in the "Exposure Assessment and Human Health Assessment" section of the TAC document even if it is assumed that exposure by this route is minimal. (Fan, April 13, 2000)

Response: The potential for dermal exposure from airborne azinphos-methyl has been discussed in the document (see last section "Uncertainties"). In short, there are no studies available that monitored dermal exposure of the general public to azinphos-methyl in the ambient air. Considering the potential for small amount of dermal exposure and the protective nature of clothing and skin, the absorbed doses from this route appear to be minute.

Comment 7: Individuals residing in rural areas near orchards and other crops to which azinphos- methyl is applied may experience repeated exposures to the relatively high airborne concentrations of this active ingredient following an application. Such exposures may occur several times or even continuously over the course of a growing season as well as over the course of many growing seasons. Therefore, we recommend that seasonal and chronic exposures and risks be estimated for this hypothetical receptor. (Fan, April 13, 2000)

Response: Repeated and continuous non-occupational exposure to the application site airborne azinphos-methyl appears to be unlikely. The application site monitoring study showed no azinphos-methyl in any samples taken one to three days after an application. In addition, azinphos-methyl may be applied only a few times, no more than six, to a specific crop during a season due to label restrictions. These applications are not continuous but rather spread over the entire season. Individuals residing near an orchard may be exposed to the application site airborne azinphos-methyl one or up to six (the most) times intermittently during a year, but not continuously. In addition, the U.S. EPA has recently reduced the maximum yearly application rate/acre to some fruit trees (apple, pear, peaches, and nectarines) by 25%. This could affect the number of applications and/or the rate of applications.

V. Department of Pesticide Regulation Staff Responses to Summarized Comments on Part C—Human Health Assessment

Comment 1: OEHHA recommends incorporating several studies from the open literature between 1994 and 1999 into Part C. (Fan, April 13, 2000)

Response: These newer studies were added. Two of these studies (Astroff and Young, 1998; Sheets *et al.*, 1997) are merely published versions of studies the registrant had submitted to DPR in more detail as required by the FIFRA guidelines (Kowalski *et al.*, 1987; Sheets and Hamilton, 1995).

Comment 2: Carrier and Brunet (1999) estimated a subacute NOEL of 0.1 mg/kg (absorbed) for peach harvesters using pharmacokinetic modeling. This NOEL should be used to evaluate repeated, short-term exposure to azinphos-methyl in ambient air. (Fan, April 13, 2000)

Response: A discussion of the study conducted by Carrier and Brunet (1999) was added to the Acute Toxicity section under Human Studies. A comparison of the estimated NOELs from this study with the acute and subchronic NOELs selected for MOE calculations was added to the Risk Appraisal. However, the NOELs that Carrier and Brunet estimated were not used to calculate any MOEs for ambient air exposure for several reasons. The primary reason is the exposure in the peach harvesters was not controlled, but estimated from urinary metabolite excretion by toxicokinetic modeling applying various assumptions about rate constants and the number of compartments. In the past, DPR has always used NOELs from studies where the exposure was controlled. Using an estimated NOEL would be precedent setting and would add more uncertainty to the risk calculations. In addition, exposure in the peach harvesters is essentially all dermal since they did not begin harvesting until 30 days after treatment. Finally, repeated exposure to azinphos-methyl in ambient air was already addressed in the calculation of an SADD and the seasonal MOEs. The Pond site in the ambient air monitoring represents a worse case scenario

because the air sampler was less than 100 meters from almond orchards to the east, south and west. As it turns out, a NOEL of 0.09 mg/kg/day was used to calculate the seasonal MOEs for ambient air. This NOEL is similar to the absorbed NOEL that Carrier and Brunet estimated for repeated exposure in harvesters. Consequently, if the NOEL estimated by Carrier and Brunet had been used instead, the seasonal MOEs for ambient air would be essentially the same.

Comment 3: For consistency, clarity and precision, the terms "plasma ChE" and/or "erythrocyte ChE" should be used instead of "blood ChE" throughout the document. (Fan, April 13, 2000)

Response: The use of the term "blood ChE inhibition" was replaced with more specific plasma and/or RBC ChE inhibition depending on which was appropriate. In addition, "erythrocyte ChE" was replaced with "RBC ChE" because of space limitations in some tables.

Comment 4: Although there may not be a clear dose-response in the incidence of diarrhea in male dogs in the one-year feeding study conducted by Allen (1990), OEHHA recommends that the NOAEL for this study be set at 0.15 mg/kg-day based on the increase in frequency of diarrhea in males at 0.688 mg/kg-day. This NOAEL would be in agreement with the NOAEL that U.S. EPA identified for this study. The recommended NOAEL of 0.15 mg/kg-day for this dog study would be the lowest NOAEL from the available chronic toxicity studies and, therefore, should be selected as the critical NOAEL for calculating chronic MOEs. (Fan, April 13, 2000)

Response: The NOEL for the 1-year dog study by Allen (1990) was changed to 0.15 mg/kg/day. The discussion of the occurrences of diarrhea was elaborated to show that in several groups (mid-dose males, control females, and high-dose females) one dog had most of these occurrences and that these same dogs also had diarrhea during the pretreatment period. This suggests some occurrences of diarrhea are unrelated to cholinesterase inhibition.

However, DPR concluded it could not state with absolute certainty that all of the occurrences of diarrhea were unrelated to cholinesterase inhibition. Therefore, DPR made a health-protective assumption that the increase in diarrhea in the mid-dose males was treatment-related. Because of the change in this NOEL, the dog study now had the lowest NOEL for overt toxicity and RBC ChE inhibition with chronic exposure. Consequently, this study was selected as the definitive study for evaluating chronic exposure to azinphos-methyl in ambient air.

Comment 5: OEHHA recommends that three newer studies (Bianchi *et al.*, 1994; Bianchi-Santamaria *et al.*, 1997; Shah *et al.*, 1997) with positive results for genotoxicity be included in the Genotoxicity section. (Fan, April 13, 2000)

Response: The three studies cited were added to the tables and discussion in the Genotoxicity section and to the Oncogenicity Weight of Evidence section.

Comment 6: The limitations of the available oncogenicity studies should be elaborated. The discussion of the NCI mouse oncogenicity study is too brief and should include the tumor incidences in the summary. The basis/assumptions used in converting the feed concentration to daily intake is not presented for some studies and appears to be different from the defaults used for the NCI studies. (Fan, April 13, 2000)

Response: A discussion of the different strains and dose levels used in the available oncogenicity studies was added to the summary of this section and to the Oncogenicity Weight of Evidence section. The discussion of the NCI mouse oncogenicity study was elaborated and a table summarizing liver tumor incidence in males was added. No assumptions were reported when feed concentration was converted to test compound intake for various feeding studies if the study report included test compound intake calculations (usually available in newer studies). These test compound intake calculations are usually considered more accurate because they use

the actual body weight, food consumption and analytical concentration of test compound when calculated. Some confusion may have arisen because the test-compound intake was averaged for both sexes and rounded to the nearest tenth of mg. Since this appears to have lead to some confusion, separate test compound intake was reported for each sex and was only rounded to the nearest hundredth of mg. It is the author's opinion that no explanation for the conversion is warranted when the values are taken directly from the reports and no assumptions were used.

Comment 7: The description of the pooled controls as concurrent controls plus historical controls is incorrect. (Fan, April 13, 2000)

Response: The use of the term "historical controls" was eliminated from the description of the pooled controls. The description of pooled controls was changed to indicate that control animals came from studies conducted at the laboratory at approximately the same time (± 3 months) using the same strain and supplier.

Comment 8: NCI concluded the increase in liver tumors in male mice was not treatment-related because it was within the historical control range. OEHHA recommends the inclusion of a discussion of lack of scientific consensus on the validity of judging tumor increases to be non-treatment-related based on comparisons of tumor incidences from treated animals with historical controls. This discussion should include the use of increased hepatocellular adenomas or carcinomas in male $B6C3F_1$ mice as a basis for assessing carcinogenicity. (Fan, April 13, 2000)

Response: Under the NCI mouse study summary, a sentence was added to indicate that the historical control range or mean was not reported for liver tumors in male mice. In the Oncogenicity Weight of Evidence section, historical control data reported by Ward (1979) for NCI studies conducted between 1972 and 1977 were discussed. In addition, a comment regarding the lack of scientific consensus on the use historical control data for evaluating

tumor incidences was added to this section. No further discussion of the high incidence of liver tumors in male B6C3F$_1$ mice was added because it is unclear if this is a unique problem to this strain of mice. The male CD-1 mice used in the other mouse oncogenicity study had a similar combined incidence of liver tumors (26%) as the historical controls for NCI B6C3F$_1$ mice from 1972 to 1977 (22%).

Comment 9: There were increases in the NCI rat oncogenicity study in several sites when compared to pooled controls, including pituitary, adrenals, thyroid, parathyroid, and pancreas. (Fan, April 13, 2000)

Response: The incidence of pituitary and parathyroid tumors was added to the table for the male rats from the NCI oncogenicity study. A discussion of these tumors was also added to the text.

Comment 10: OEHHA recommends removing the word "slightly" from the description of the statistical significance in the trend test for male rat pancreatic islet cell tumors when compared to matched controls in the NCI study. (Fan, April 13, 2000)

Response: The word "slightly" was removed from the sentence discussing the statistical significance of pancreatic islet cell tumors in male rats in the NCI study.

Comment 11: OEHHA recommends additional discussion be added to this section regarding the NCI studies and the use of control animal data. OEHHA does not believe the results from these studies should be dismissed for the reasons stated in the draft TAC document. In addition, greater detail on the relative strengths and weaknesses of all of the oncogenicity studies should be provided. (Fan, April 13, 2000)

Response: The discussion of the strengths and weaknesses of all of the oncogenicity studies was expanded, especially with respect to the deficiencies with the NCI studies. At the time, further discussion of the NCI studies did not

seem warranted since both U.S. EPA and JMPR placed greater importance on the newer oncogenicity studies that met FIFRA guidelines in their evaluation of the oncogenic potential of azinphos-methyl.

Comment 12: OEHHA agrees that the total body of evidence available thus far does not indicate that a cancer potency and unit risk factor should be developed for azinphos-methyl. The spectrum of tumors in the NCI rat study indicates a potential endocrine effect, although a mechanism is not apparent and has not been supported by other studies. (Fan, April 13, 2000)

Response: A discussion of a possible endocrine effect was added with respect to the increase in tumors in male rats in the NCI study. It was pointed out, as OEHHA stated, that a mechanism for this apparent endocrine effect is unknown and not supported by the other rat oncogenicity studies. However, the higher dose level in the NCI study may have resulted in sufficient cholinesterase inhibition to cause endocrine disruption.

Comment 13: While the available cancer bioassay data do not warrant the calculation of a potency slope or unit risk factor for azinphos-methyl, the results of these studies should not be dismissed. (Fan, April 13, 2000)

Response: The brief discussion of the NCI studies was not intended to dismiss these studies, but that the evidence from these studies was considered of limited usefulness based on the study design which made interpretation of these findings difficult.

Comment 14: OEHHA noted that the term “Reference Exposure Level” was used in the Table of Contents and “Reference Concentration” in the body of the report. OEHHA recommends that to the RELs for chronic exposure be recalculated based on the suggested critical NOEL for chronic toxicity and that this section be expanded to include a comparison with exposure levels. (Fan, April 13, 2000)

Response: The identification of the Reference Concentration section in the Table of Contents as “Reference Exposure Levels” was in error. DPR has decided to use the term reference concentration rather than reference exposure levels because they are calculated slightly different. DPR adjusts the air concentration based on the breathing rate of children which OEHHA does not. The reference concentration for chronic exposure was recalculated based on the new chronic NOEL. DPR has not previously calculated hazard indices in their toxic air contaminant documents. However, a comparison of the reference concentrations with the highest concentrations detected in offsite and ambient air was added to the discussion